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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,749	01/14/2002	Michael Vajdy	16464.003	5494

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/051,749	VAJDY ET AL.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-30 and 35-42* is/are pending in the application.

4a) Of the above claim(s) *6,7,22-28 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-17, 19-21, 29-30, 35-39 and 41-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 18 and 31-34 are cancelled. Claims 35-42 are added. Claims 1-17, 19-30 and 35-42 are pending. Claims 6-7 and 22-28 are withdrawn from examination for being directed to a nonelected invention. Additionally, claim 40 is also withdrawn from examination for being directed to a nonelected species, wherein Applicant has elected HIV as the antigen for examination in Applicant's April 05, 2004 reply. Claims 1-5, 8-17, 19-21, 29-30, 35-39 and 41-42 are under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-5, 8-17, 19-21, 29-30, 35-39 and 42 are rejected under 35 U.S.C. 103(a) as being obvious over Malone et al.[1] in view of Barchfeld et al.,[2] as evidenced by Rappuoli, R.[3]

In response to the rejection, Applicant argues that the Office fails to make a prima facie case that the claimed invention is obvious because the Office fails to articulate any reason why a skilled artisan would, in view of the prior art, have arrived at the claimed invention. Specifically, Applicant argues that there is no teaching or

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[1] Malone et al. U.S. Pat. No. 6110898, filed 05/23/1997.
[2] Barchfeld et al., WO 98/42375, published 10/01/1998.

suggestion in Malone to include ADP-ribosylating toxin in protein form. Applicant notes that Malone teaches that DNA encoding ADP-ribosylating toxins can be incorporated into a vector. In view of this, Applicant additionally argues that Malone teaches away from the claimed invention because while "Malone knew that ADP-ribosylating toxins functioned as mucosal adjuvants…he suggests using them only as nucleotide sequences in DNA vaccines" and further argues that neither Barchfeld nor Rappuoli cures Malone's deficiency.

Applicant's arguments have been considered, however, it is not found persuasive. Applicant's argument that there is no teaching or suggestion in Malone to use ADP-ribosylating toxin in protein form is not persuasive for, and as acknowledged by Applicant, Malone teaches that ADP-ribosylating toxins are mucosal adjuvants. Regarding Applicant's teaching away argument, while Malone does disclose that the vector may contain a gene encoding an adjuvant, such as the cholera toxin, it should be noted that such teachings is not a teaching away. MPEP 2123 (II) states, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In the instant case, Malone merely discloses different embodiments of his invention. In addition to disclosing the insertion of gene encoding ADP-ribosylating toxins into a vector, Malone also discloses that adjuvants, including ADP-ribosylating toxins can be used with the vectors. [Line 63, column 10 to line 13, column 11, in particular.] MPEP 2123 (II) also provides, the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of

[3] Rappuoli, R. WO 95/17211, published 06/29/1995.

these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." In the instant case, Malone does not criticize, discredit, or otherwise discourage the use of ADP-ribosylating toxins as mucosal adjuvants. Hence, while Applicant's teaching away argument has been considered, it is not found persuasive.

The claims are directed to a method of generating an immune response in a subject comprising mucosal administration of a composition comprising a detoxified bacterial ADP-ribosylating toxin and a replication defective gene delivery vehicle comprising a polynucleotide encoding at least one antigen. Claims 2-4, which depend on claim 1, require the mucosal administration be intranasal, intrarectal and intravaginal, respectively. Claim 5, which depends on claim 1, requires the antigen be derived from a sexually transmitted pathogen, which is limited to a virus by claim 8. Claims 9 and 10 limit the virus to HIV-1. Claim 11, which depends on claim 1, requires the gene delivery vehicle be selected from the group consisting of a nonviral vector, a viral vector, a particulate carrier and a liposome preparation. Claim 12, limits the vehicle to a viral vector selected from a group consisting of a retroviral vector, an adenoviral vector, a poxvirus vector, a picornavirus vector and an alphavirus vector. Claim 13, which depends on claim 12, limits the viral vector to a Sindbis vector, which is an alphavirus vector. Claim 14, which depends on claim 12, limits the viral vector to an alphavirus selected from a group consisting of Semliki Forest virus, Venezuelan equine encephalitis virus and Ross River virus vector. Claim 15 requires the alphavirus vector of claim 12, which depends on claim 11, to comprise sequences from two or more

alphaviruses. Claim 16, requires the viral vector be an alphavirus vector that is delivered to antigen presenting cell, which is limited to dendritic cells by claim 17. Claim 19, which depends on claim 1, requires the immune response elicited be HLA class I-restricted, which is limited to a HLA Class II-restricted immune response by claim 20. Claim 21, which depends on claim 1, requires the method of claim 1 to further comprise introducing into target cells of the subject a nucleic acid molecule that encodes at least a protein selected from the group consisting of Class I MHC protein, Class II MHC protein, CD3, ICAM-1, LFA-3. Claims 29-30, which depend on claims 13 and 15, respectively, require the alphavirus vector contained in an alphavirus replicon particle. Claim 35, which depends on claim 1, requires the detoxified toxin be selected from the group consisting of a cholera toxin, a pertussis toxin, and an *E.coli* heat labile toxin. Claims 36-39, which depend on claim 35, limit the toxin to LT-K63, LT-R72, CT-S109 and PT-K9/G129. Claim 42, which depends on claim 1, requires the vehicle be administered according to a multiple dose schedule.

As established in the previous office action, mailed 09/21/2005, Malone teaches a method of inducing a mucosal immune response wherein an antigenic polynucleotide is administered to the vaginal, nasal or rectal mucosal membranes of a subject according to a multiple dose schedule. [Abstract, lines 2-4; col. 14, lines 64-66; col. 15, lines 57-62; and col. 17, lines 14-17 and 61-63, in particular.] Malone et al. teaches that the antigenic polynucleotide may be derived from a sexually transmitted virus such as HIV-1. [Col. 20, lines 7-10 and 23-25, in particular.] Malone et al. further teaches that the polynucleotide be delivered by an alphaviral vector such as Sindbis or Semliki

Forest virus. [Col. 11, lines 39-41, in particular.] The alphavirus vector used by Malone et al. comprises a replicon. [Col. 2, line 66 to col. 3, line 1, in particular.] Malone et al. also discloses introducing a nucleic acid that encodes a Class I and/or a Class II MHC protein. [Col. 4, lines 60-65, in particular.]

The difference between the claimed invention and the disclosure of Malone et al. is: Malone et al. does not teach the administration of a detoxified bacterial ADP-ribosylating toxin, which are adjuvants. However, it should be noted that Malone et al. does teach the use of adjuvants with his replication defective gene delivery vehicle. [Col. 3, line 61 to col. 4, line 3 and 36-47, in particular.] At the cited passage, Malone et al. suggests the use of detoxified bacterial ADP-ribosylating toxin as an adjuvant, including *E. coli* and cholera toxins.

While Malone et al. does suggest the use of an E.coli heat labile toxin as an adjuvant, Malone et al. does not teach the following toxins: LT-K63, LT-R72, CT-S109 and PT-K9/G129. However, the deficiency noted of Malone et al. is fully compensated by Barchfeld et al.

Barchfeld et al. teaches LT-K63, LT-R72, CT-S109, and PT-K9/G129. Barchfeld et al. teaches the use of these detoxified toxins as adjuvants. [Lines 15-20, page 5, in particular.] Barchfeld et al. discloses the adjuvants are mucosal adjuvants, as evidenced by Rappuoli, R. Rappuoli, R. teaches that the non-toxic mutants of the toxins are active as mucosal adjuvants.

Hence, at the time the invention was made, the use of LT-K63, LT-R72, CT-S109, and PT-K9/G129 as adjuvants are well known in the art. It would have been

prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to substitute the adjuvant of Malone et al. with the adjuvants of Barchfeld et al. (K63, LT-R72, CT-S109, and PT-K9/G129). At the time the invention was made, one of ordinary skill in the art would have been motivated to do so to enhance the immune response induced by the composition of Malone et al. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the substitution of equivalents, adjuvants, are routinely practiced in the art.

It should be noted that Malone et al. inherently discloses presenting an antigenic polynucleotide to dendritic cells. This is necessarily so because mucosal membranes are a natural environment for dendritic cells. Thus, by introducing an antigenic polynucleotide to a mucosal surface, Malone et al. necessarily discloses presenting the antigenic polynucleotide to dendritic cells.

Additionally, as previously noted, Malone et al. inherently teaches eliciting an HLA class I or HLA class II response. This results because Malone et al. teaches administering the antigen-encoding polynucleotide to a human, which would necessarily cause an HLA class I and HLA class II response.

Regarding claim 15, neither Malone et al. nor O'Hagan et al. teaches the invention encompassed by claim 15. However, this limitation provides that a sequence from the alphavirus gene delivery vehicle, such as a promoter, may be substituted with a sequence from an alphaviruses of a different serotype. Whether the gene delivery vehicle is derived from one or two alphavirus genomes is immaterial since both

embodiments would have similar structure and function. Thus, modifying the gene delivery vehicle of Malone et al. to include a second alphavirus construct would have been obvious to one of ordinary skill in the art, at the time the invention was made. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to determine a workable or optimal gene delivery vehicle. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because substitution of known equivalents are routinely practiced in the art.

4. Claims 1 and 41 are rejected under 35 U.S.C. 103(a) as being obvious over Malone et al., in view of Barchfeld et al., as evidenced by Rappuoli, R., in further view of McCluskie et al.[4]

In response to the rejection, Applicant argues that McCluskie fails to remedy the deficiency noted in Malone, Barchfeld and Rappuoli, presented in paragraph 3 of this office action.

Applicant's argument has been considered, however, it is not found persuasive for the reason(s) set forth in paragraph 3 of this office action.

Claim 41, which depends on claim 1, requires the composition to further comprise a CpG oligonucleotide.

Neither Malone et al. nor Barchfeld et al. teaches the addition of a CpG oligonucleotide. However, at the time the invention was made, McCluskie et al. teaches

[4] McCluskie et al. Cutting Edge: CpG DNA is a potent enhancer of systemic and mucosal immune responses against hepatitis B surface antigen with intranasal administration to mice. The Journal of Immunology, 1998, Vol. 161, 4463-4466.

that CpG oligonucleotide is a potent enhancer of systemic and mucosal immune responses. McCluskie et al. also discloses that combined with another mucosal adjuvant, such as cholera toxin, the oligonucleotide and toxin act synergistically, giving stronger responses than those observed with 10 times more of either adjuvant alone. Hence, at the time the invention was made, to combine the teachings of Malone et al., Barchfeld et al. and McCluskie et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do to induce a strong immune response against the antigen of Malone et al. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the synergistic combination of the oligonucleotide and mucosal adjuvants such as cholera toxins has been demonstrated by McCluskie et al.

Conclusion

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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